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Week 96 results of a phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients

Chloe Orkin[a], Joseph J. Eron[b], Jürgen Rockstroh[c], Daniel Podzamczer[d], Stefan Esser[e], Linos Vandekerckhove[f], Erika Van Landuyt[g], Erkki Lathouwers[g], Veerle Hufkens[g], John Jezorwski[h], Magda Opsomer[g], on behalf of the AMBER study group

Background: Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg was investigated through 96 weeks in AMBER (NCT02431247).

Methods: Treatment-naive, HIV-1-positive adults [screening plasma viral load ≥1000 copies/ml; $CD4^+$ cell count >50 cells/μl) were randomized (1 : 1) to D/C/F/TAF ($N = 362$) or D/C plus emtricitabine/tenofovir-disoproxil-fumarate (F/TDF) ($N = 363$) over at least 48 weeks. After week 48, patients could continue on or switch to D/C/F/TAF in an open-label extension phase until week 96.

Results: At week 96, D/C/F/TAF exposure was 626 patient-years (D/C/F/TAF arm) and 109 patient-years (control arm post switch), week 96 virologic suppression (viral load <50 copies/ml; FDA-Snapshot, from baseline) was 85.1% (308/362) (D/C/F/TAF) and 83.7% (304/363) (control). Week 96 virologic failure (viral load ≥50 copies/ml; FDA-Snapshot) was 5.5% (20/362) and 4.4% (16/363), respectively. No darunavir, primary protease inhibitor or tenofovir resistance-associated mutations (RAMs) were observed post baseline. In one patient in each arm, an M184I and/or V RAM was detected. Few adverse event-related discontinuations (3% D/C/F/TAF; <1% control post switch) and no deaths occurred on D/C/F/TAF. Improved renal and bone parameters were maintained in the D/C/F/TAF arm and observed in the control arm post switch. Increases in total-cholesterol/high-density-lipoprotein–cholesterol rtio at week 96 were +0.25 versus baseline (D/C/F/TAF) and +0.24 versus switch (control).

Conclusion: At week 96, D/C/F/TAF resulted in high virologic response and low virologic failure rates, with no resistance development to darunavir or TAF/TDF. Bone, renal and lipid safety were consistent with known D/C/F/TAF component profiles. Control arm safety post switch was consistent with the D/C/F/TAF arm. AMBER week 96 results confirm the efficacy, high barrier to resistance and bone/renal safety benefits of D/C/F/TAF for treatment-naive patients.

AIDS 2020, **34**:707–718

Keywords: ART-naive, darunavir/cobicistat/emtricitabine/tenofovir alafenamide, efficacy, safety, single-tablet regimen

[a]Department of Infection and Immunity, Queen Mary University, London, UK, [b]Department of Medicine, The University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA, [c]Department of Medicine I, University Hospital Bonn, Bonn, Germany, [d]Infectious Diseases Department, IDIBELL-Hospital Universitari de Bellvitge, L'Hospitalet, Barcelona, Spain, [e]Department of Dermatology and Venerology, University Hospital Essen, Essen, Germany, [f]Department of Internal Medicine and Pediatrics, Ghent University and Ghent University Hospital, Ghent, [g]Janssen Pharmaceutica NV, Beerse, Belgium, and [h]Janssen Research & Development, Pennington, New Jersey, USA.

Correspondence to Chloe Orkin, Department of Infection and Immunity, Royal London Hospital and Queen Mary University, Barts Health NHS Trust, London E1 1BB, UK.

E-mail: c.m.orkin@qmul.ac.uk

Received: 9 August 2019; revised: 20 November 2019; accepted: 3 December 2019.

DOI:10.1097/QAD.0000000000002463

Introduction

Combination antiretroviral therapy (ART) regimens with long-term safety and efficacy, a high genetic barrier to resistance and convenience are required for sustained virological success in the treatment of HIV-1 infection. Since 2006, substantial clinical trial data and clinical experience has accumulated for boosted darunavir (DRV), demonstrating its durable virologic response, high genetic barrier to resistance and long-term safety [1–6].

Current combination ART regimens provide high and sustained antiviral efficacy, are well tolerated and have a low pill burden. However, developing better tolerated and more convenient regimens, while maintaining a high genetic barrier to resistance, is important. Once-daily, single-tablet regimens (STRs) improve patient satisfaction and may improve treatment adherence and virologic suppression compared with multitablet regimens [7–9]. A once-daily STR, darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg, currently approved in Europe, the United States and Canada [10,11], is being investigated in two international, randomized, phase 3 studies, AMBER [5] and EMERALD [6]. D/C/F/TAF is currently the only STR that includes a boosted protease inhibitor (bPI).

Week 48 primary analyses of both trials showed that D/C/F/TAF had high, noninferior antiviral efficacy with better outcomes for D/C/F/TAF bone and renal safety parameters versus D/C plus emtricitabine/tenofovir disoproxil fumarate (F/TDF) in ART-naive adults in AMBER [5] and versus bPI with F/TDF in ART-experienced, virologically suppressed adults in EMERALD, including those with a history of non-DRV virologic failure [6]. In EMERALD, antiviral efficacy was maintained through week 96 in the D/C/F/TAF arm [12].

D/C/F/TAF STR or boosted DRV 800 mg once-daily given in combination with two nucleoside or nucleotide analogue reverse transcriptase inhibitors (N(t)RTIs) is recommended as a first-line treatment option in the EU [13] and in the United States for patients who may have uncertain adherence, who require a regimen with a high genetic barrier to resistance, or who may not have resistance results available, such as those who are rapidly starting treatment [14,15].

The efficacy, safety and resistance results for D/C/F/TAF through week 96 in AMBER are presented.

Methods

Study design and patients

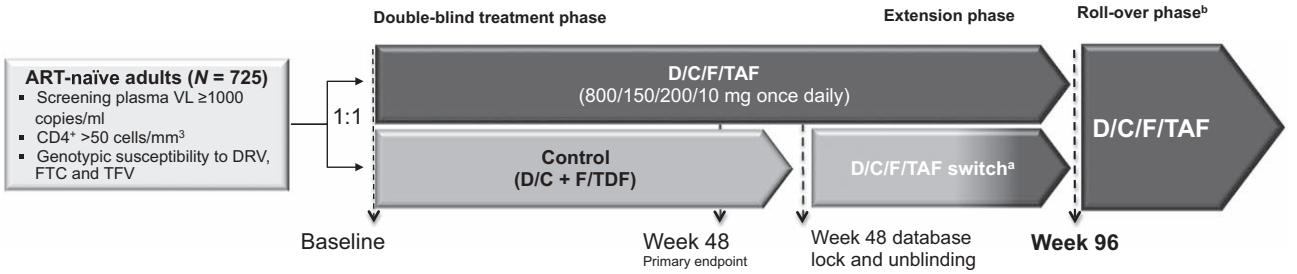
AMBER (TMC114FD2HTX3001; NCT02431247) is a phase 3, randomized, active-controlled, double-blind, noninferiority study conducted at 121 sites across 10 countries in North America (USA, Canada) and Europe (Belgium, France, Germany, Italy, Poland, Russia, Spain, UK) [5]. The study included ART-naive adults with HIV-1 and a screening plasma viral load at least 1000 copies/ml (COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, V2.0; Roche Diagnostics, Basel, Switzerland) [5], $CD4^+$ cell count greater than 50 cells/μl and genotypic sensitivity to DRV, emtricitabine and tenofovir (Sanger sequencing) (Fig. 1).

Patients were randomized (1 : 1) to receive D/C/F/TAF 800/150/200/10 mg once daily or D/C 800/150 mg fixed-dose combination (FDC) co-administered with F/TDF 200/300 mg FDC once daily (control arm) over at least 48 weeks. After week 48 database lock and unblinding, patients could continue on or switch to D/C/F/TAF (D/C/F/TAF switch) in an open-label, single-arm extension phase until week 96, with study visits every 12 weeks. Patients switched to D/C/F/TAF at different time points (not uniformly) as switch could only occur after all patients reached week 48 and the database was locked. Therefore, individual duration of exposure to D/C/F/TAF was variable (Fig. 1).

Study endpoints

The primary outcome was noninferiority of D/C/F/TAF versus control for the proportion of patients with viral load less than less 50 copies/ml (response rate; FDA-snapshot analysis) at week 48 (10% margin). Secondary efficacy endpoints at week 96 included the proportion of patients with viral load less than 50 copies/ml (and at least 50 copies/ml, virologic failure category by FDA-snapshot), viral load less than 200 copies/ml and at least 200 copies/ml (FDA snapshot) and less than 50 copies/ml [time to loss of virologic response (TLOVR) algorithm], and changes from baseline in $CD4^+$ cell count. Given the nonuniform switch times, and therefore, nonuniform D/C/F/TAF exposure post switch, there was no comparator treatment arm after the baseline-week 48 phase. As such, efficacy for the overall week 96 control arm (e.g. irrespective of treatment from baseline to week 96) is shown in the main results. However, efficacy data for D/C/F/TAF switch-week 96 are shown in the supplementary material (http://links.lww.com/QAD/B598).

Other secondary endpoints included post baseline resistance (genotype/phenotype) (PhenoSense GT; combined HIV-1 PR/RT genotype/phenotype [5]) of protocol-defined virologic failures (PDVFs; virologic nonresponse, virologic rebound, and/or viraemic at final time point) with viral load at least 400 copies/ml at failure or at later time points [5], treatment adherence, adverse event incidences and body weight, changes in serum creatinine, estimated glomerular filtration rate based on serum creatinine ($eGFR_{cr}$) [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [16]], eGFR based on



	D/C/F/TAF arm N = 362	Control arm N = 363	
		D/C + F/TDF N = 363	D/C/F/TAF switch N = 295
Patient-years of exposure[c]	626	512	109
Median (IQR) exposure, weeks[d]	96.1 (95.6; 97.0)	73.1 (72.0; 84.3)	22.3 (12.1; 24.3)

Fig. 1. AMBER study design. ART, antiretroviral therapy; D/C + F/TDF, darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate once daily; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide once daily; DRV, darunavir; FTC, emtricitabine; IQR, interquartile range; TFV, tenofovir; VL, viral load. [a]Patients switched to D/C/F/TAF at different time points (not uniformly) leading to a lack of uniform D/C/F/TAF exposure post switch. [b]After week 96, participants were given the opportunity to remain in the trial until the study drug became commercially available. [c]Patient-years of exposure = sum of treatment duration (weeks) × 7/365.25. [d]Treatment duration, weeks = (end of treatment phase – start of treatment phase + 1)/7.

cystatin C ($eGFR_{cyst}$, CKD-EPI formula [16]) and ratios of total urine protein, urine albumin, fasted retinol binding protein and fasted β-2-microglobulin to creatinine (UPCR, UACR, RPB:Cr and B2M:Cr, respectively). Deep sequencing using next-generation sequencing GenoSure MG (Illumina MiSeq; codon variants >1%) was to be performed retrospectively on baseline samples from patients with HIV-1 viruses that showed emerging resistance-associated mutations (RAMs).

Endpoints in the bone investigation substudy were percentage change from baseline in hip, lumbar spine and femoral neck bone mineral density (BMD) measured by DXA scans, changes in associated *T*-score (normal BMD defined as a *T* score ≥ -1; osteopenia as a *T* score from ≥ -2.5 to < -1; and osteoporosis as a *T*-score < -2.5), and changes in bone biomarkers.

Statistical analysis

The main outcome analysis was based on the intention-to-treat (ITT) population, constituting all randomized patients who received at least one dose of study drug. A per-protocol analysis was also performed, excluding patients with major protocol violations, those with no post baseline viral load measurement or treatment adherence less than 65%. Secondary efficacy endpoints were described using descriptive statistics.

Data analysis was performed using SAS software (SAS Institute, Inc, Cary, North Carolina, USA) version 9.2. Least square mean change from reference at week 96 in $CD4^+$ cell count (noncompleter equalled failure; last observation was carried forward otherwise) and associated 95% confidence intervals (CIs) were evaluated with ANCOVA, adjusting for baseline $CD4^+$ cell count separately by treatment arm.

Treatment adherence was measured by drug accountability (based on pill count) cumulative from baseline to switch and from switch to open-label D/C/F/TAF through week 96 for patients who returned all dispensed bottles. Within treatment arm comparisons of adherence (>95% versus ≤95%) during baseline to switch and D/C/F/TAF during switch to week 96 were performed using McNemar's Exact Test.

Within-treatment arm comparisons for change at week 96 from reference were assessed by Wilcoxon signed-rank test for eGFR, renal biomarkers and fasting lipids and by paired *t*-test for BMD. Reference for the D/C/F/TAF arm was study baseline and for the control arm (D/C/F/TAF switch) through week 96 was the last value before the switch.

Results

Baseline characteristics and patient disposition

Baseline patient demographic characteristics and disease characteristics were reported previously [5], and are included in Supplementary Table 1, http://links.lww.com/QAD/B598. At screening, all enrolled patients

showed genotypic sensitivity to DRV, emtricitabine and tenofovir based on the genotype report.

Of 362 patients in the D/C/F/TAF arm, 335 continued receiving D/C/F/TAF in the trial after week 48 and 319 of 362 (88%) reached week 96, of whom six of 319 completed the study and 313 of 319 are ongoing (Fig. 2). Of 363 patients in the control arm, 295 switched to D/C/F/TAF by week 96 and 290 of 363 (80%) reached week 96, with seven of 290 completing the study and 283 of 290 ongoing (Fig. 2). The most common reasons for discontinuing the study after week 48 in the D/C/F/TAF arm, as indicated by the investigator, were withdrawal of consent, lost to follow-up and physician decision (Fig. 2).

Treatment exposure through week 96

At week 96, exposure to D/C/F/TAF was 626 patient-years in the D/C/F/TAF arm, and consecutively 512 patient-years to D/C plus F/TDF and 109 patient-years to D/C/F/TAF in the control arm (Fig. 1). Post switch to D/C/F/TAF in the control arm, 294 of 295 patients (99.7%) had exposure to D/C/F/TAF for at least 4 weeks, 252 for at least 12 weeks (85.4%), 102 for at least 24 weeks (34.6%) and two for at least 36 weeks (0.7%). The median time from week 48 to switch was 26 weeks.

Efficacy analyses

In the D/C/F/TAF arm, 85.1% of patients (308 of 362) had virologic suppression at week 96 (viral load <50 copies/ml; ITT FDA-snapshot analysis) (Fig. 3a and Supplementary Table 2, http://links.lww.com/QAD/B598). The week 96 response rate (from baseline) in the overall control arm was 83.7% (304/363) (Fig. 3a and Supplementary Table 2, http://links.lww.com/QAD/B598). Viral load at least 50 copies/ml (virologic failure category; ITT FDA snapshot) at week 96 occurred in 20 of 362 (5.5%) patients in the D/C/F/TAF arm and 16 of 363 (4.4%) in the overall control arm (Fig. 3a and Supplementary Table 2, http://links.lww.com/QAD/B598).

Week 96 virologic responses were similar in the per-protocol FDA-snapshot analysis (87.9%, 297 of 338 D/C/F/TAF arm and 87.7%, 291 of 332 overall control arm achieved viral load <50 copies/ml), ITT-TLOVR analysis (85.1%, 308/362 D/C/F/TAF arm and 82.4%, 299 of 363 overall control arm achieved viral load <50 copies/ml) and the ITT FDA-snapshot analysis using the viral load <200 copies/ml cut off (86.2%, 312 of 362 D/C/F/TAF arm and 86.0%, 312 of 363 overall control arm achieved viral load <200 copies/ml) (Fig. 3b and Supplementary Table 2, http://links.lww.com/QAD/B598). Week 96 ITT FDA-snapshot outcomes (viral load <50 and ≥50 copies/ml) were also consistent across age, sex, race, baseline $CD4^+$ cell count and baseline viral load subgroups (Supplementary Table 3, http://links.lww.com/QAD/B598). Results for certain subgroups (baseline $CD4^+$ cell count less than 200 cells/μl and Black/African American race), should be interpreted with caution because of small sample sizes.

Immunologic response

Least squares mean (95% CI) increases ($P < 0.0001$) from baseline in $CD4^+$ cell count at week 96 were 228.9 (205.3; 252.4) cells/μl in the D/C/F/TAF arm and 226.5 (204.6; 248.5) cells/μl in the overall control arm.

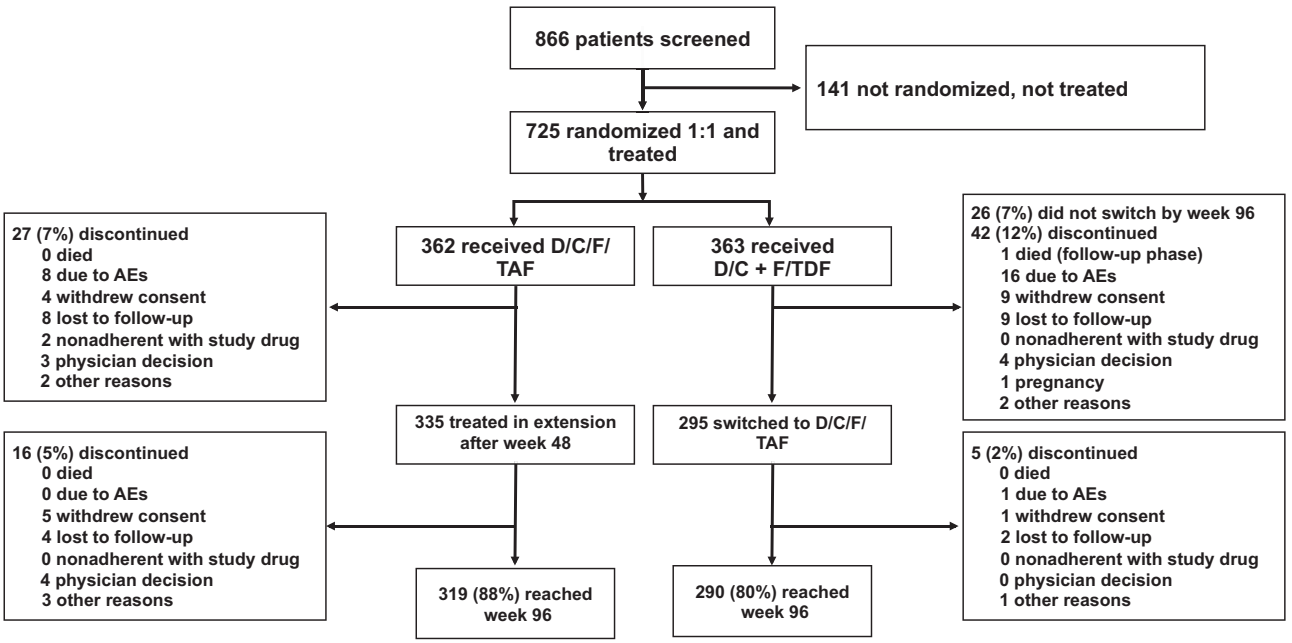
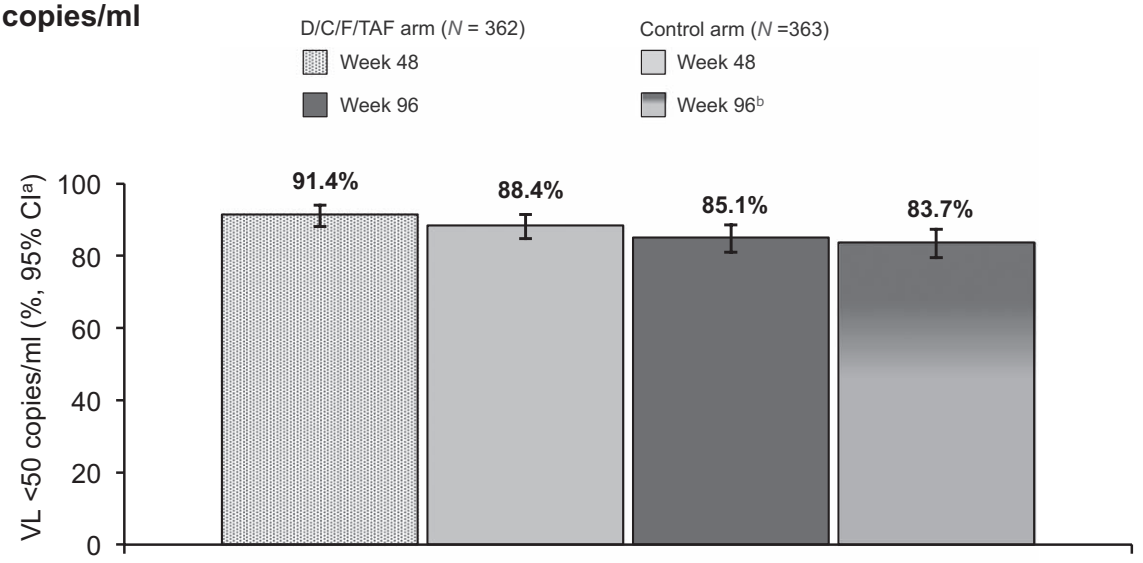


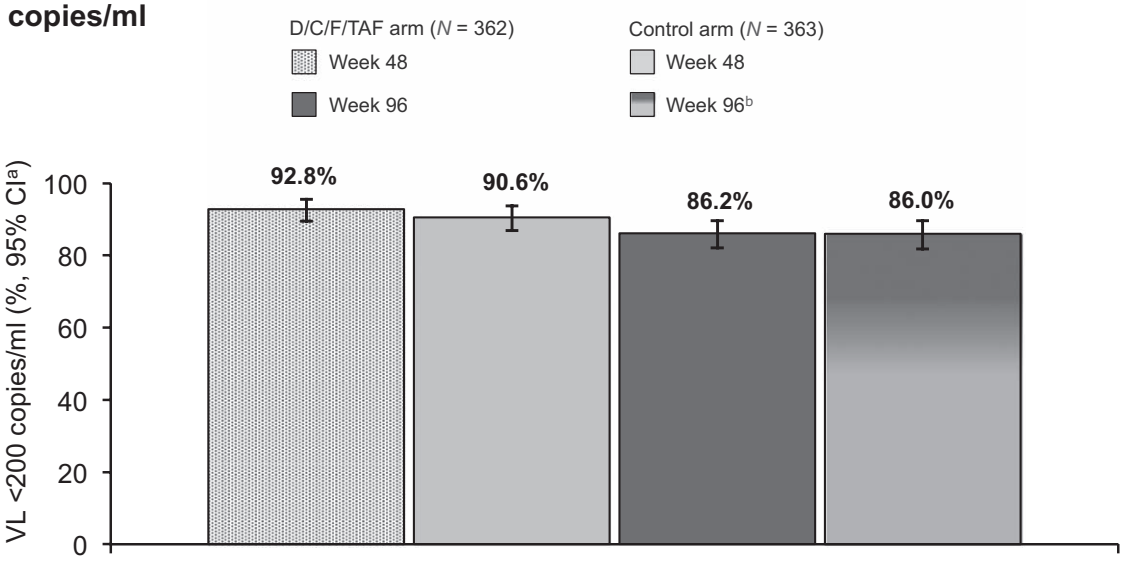
Fig. 2. Patient disposition for AMBER through 96 weeks. AE, adverse event; D/C + F/TDF, darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate once daily; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide once daily.

(a) **VL <50 copies/ml**



Virologic response (VL <50 copies/ml)	331 (**91.4%**)	321 (**88.4%**)	308 (**85.1%**)	304 (**83.7%**)
VL ≥50 copies/ml[c]	16 (**4.4%**)	12 (**3.3%**)	20 (**5.5%**)	16 (**4.4%**)
No virologic data	15 (**4.1%**)	30 (**8.3%**)	34 (**9.4%**)	43 (**11.8%**)

(b) **VL <200 copies/ml**



Virologic response (VL <200 copies/ml)	336 (**92.8%**)	329 (**90.6%**)	312 (**86.2%**)	312 (**86.0%**)
VL ≥200 copies/ml[d]	10 (**2.8%**)	4 (**1.1%**)	15 (**4.1%**)	6 (**1.7%**)
No virologic data	16 (**4.4%**)	30 (**8.3%**)	35 (**9.7%**)	45 (**12.4%**)

Fig. 3. FDA-snapshot analysis at weeks 48 and 96. (a) Less than 50 copies/ml and (b) less than 200 copies/ml (intent-to-treat). AE, adverse event; CI, confidence interval; D/C + F/TDF, darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate once daily; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide once daily; VL, viral load. [a]Two-sided Exact Clopper-Pearson 95% CI. [b]The gradient shading of the week 96 control bar represents patients switching to D/C/F/TAF at different time points after week 48 leading to variable D/C/F/TAF exposure post switch. [c]Last VL in the week 48 or week 96 window at least 50 copies/ml, or discontinuations for efficacy reasons, or premature discontinuations not because of efficacy, AEs or death with a last VL at least 50 copies/ml. [d]Last VL in the week 48 or week 96 window at least 200 copies/ml, or discontinuations for efficacy reasons, or premature discontinuations not due to efficacy, AEs or death with a last viral load at least 200 copies/ml.

Adherence to treatment

The at least 95% adherence rate as measured by pill count from baseline to switch was 87.2% (252/289 patients) in the D/C/F/TAF arm and 82.6% (233 of 282) in the control arm, with numerically, but not significantly, higher adherence after switch to open-label D/C/F/TAF STR [90% (233/259); $P = 0.34$ improved adherence] in the D/C/F/TAF arm and significantly higher adherence after switch [90% (225 of 250); $P = 0.0046$) in the control arm, both switching from three pills (double-blind) to one pill.

Resistance analysis

Through week 96, PDVF occurred in 15 (D/C/F/TAF arm) and 19 participants (control arm). Paired screening and post baseline on-treatment genotypes were available for nine and eight patients, respectively.

No DRV, primary protease inhibitor or tenofovir RAMs [17] were seen post baseline in any participant in either arm.

The emtricitabine RAM M184I/V, conferring emtricitabine and lamivudine resistance, was detected at week 36 in one patient who discontinued due to treatment noncompliance in the D/C/F/TAF arm as reported previously [5,18]. M184V was detected pretreatment as a minority variant (9%) in this patient [5,18]. M184V was detected at week 84 (after switch to D/C/F/TAF) in one patient in the control arm, but M184V was not detected pretreatment by deep sequencing. No pharmacokinetic data are available for this patient.

Safety and tolerability

D/C/F/TAF was well tolerated through 96 weeks, and safety findings at week 96 were consistent with those at week 48 (Table 1). Few adverse event-related discontinuations [3% (10 of 362)] occurred through 96 weeks in the D/C/F/TAF arm and in the control arm [<1% (one of 295)], following switch (Table 1). No deaths occurred during the treatment phase.

The most common study drug-related adverse events were diarrhoea, rash and nausea, and all were grade 1 or 2 (Table 1). Grade 1 study drug-related diarrhoea occurred in 27 of 34 patients and grade 2 in seven of 34 patients in the D/C/F/TAF arm through 96 weeks. Episodes of study drug-related diarrhoea were mostly transient in duration. Only two patients in the D/C/F/TAF arm and one in the control arm discontinued the study because of diarrhoea before week 48, with no further discontinuations after week 48 and prior to the week 96 analysis cut-off date. No neuropsychiatric study drug-related adverse events greater than 5% or related discontinuations or discontinuations because of bone or renal adverse events occurred.

Most adverse events, irrespective of causality, were grade 1 or 2. The most frequent grade 3 or 4 AE (≥2 patients) in the D/C/F/TAF arm was increased low-density lipoprotein-cholesterol (LDL-C), reported for four patients before week 48 and two patients after week 48 (both ≤1%; median 46% increase in LDL-C from baseline for the six cases). The most frequent grade 3 or 4 adverse events in the control arm post switch through week 96 were two cases of grade 3 hepatitis A and two cases of grade 4 increased aminotransferase and alanine aminotransferase (all <1%); none of which led to discontinuation. Serious adverse events considered possibly related to study drug by the investigator occurred in only one patient in the D/C/F/TAF arm (<1%) (back pain and haematuria) and did not occur in the control arm after D/C/F/TAF switch.

Renal adverse events regardless of causality occurred in 5% (17/362) of patients (D/C/F/TAF arm), with dysuria ($n = 4$), haematuria ($n = 3$), renal colic and urethral discharge (each $n = 2$) occurring in at least two patients. Renal adverse events did not occur in the control arm after D/C/F/TAF switch. No renal adverse events suggested treatment-emergent proximal renal tubulopathy. No cases of Fanconi syndrome occurred in either arm.

Median (IQR) change in body weight at week 96 was 2 (−0.3 to 5) kg in the D/C/F/TAF arm versus baseline and 1 (0 to 2.9) kg in the control arm versus last value before switch.

Laboratory parameters

Laboratory abnormalities were mostly grade 1 or 2. The most frequent (>3%) grade 3 or 4 laboratory abnormality, regardless of whether reported as an adverse event as described above, was fasting LDL-C (≥190 mg/dl) in the D/C/F/TAF arm [9% (30/362)] and control arm after D/C/F/TAF switch [4% (11/295)] (Table 1).

In the D/C/F/TAF arm, fasting lipid parameters showed stable to small increases from week 48 to week 96 (Table 1 and Supplementary Figure 1, http://links.lww.com/QAD/B596). In the control arm, similar trends were seen for increases in fasting lipids at week 96 versus reference (last value before switch) as in the D/C/F/TAF arm at week 48 versus baseline (Table 1). The change from baseline to week 96 in total cholesterol/HDL-C ratio was +0.25 in the D/C/F/TAF arm and from reference to week 96 was +0.24 in the control arm. In the D/C/F/TAF arm, lipid-lowering drugs were newly started by seven (2%) and 14 (4%) of patients by weeks 48 and 96, respectively, and in the control arm following D/C/F/TAF switch by three (1%) patients by week 96.

In the D/C/F/TAF arm, median (IQR) change from baseline to week 96 in $eGFR_{cr}$ (CKD-EPI formula; [16]) was −5.6 (−12.8 to 0.1) ml/min per 1.73 m^2 ($P < 0.001$) (Fig. 4a). Median (IQR) change to week 96 versus reference in $eGFR_{cr}$ was +2.3 (−3.4 to 9.7) ml/min per 1.73 m^2 in the control arm ($P < 0.001$). Only 22 patients at

Table 1. Overview of treatment-emergent adverse events and laboratory abnormalities and median (interquartile range) change from baseline in lipids.

	D/C/F/TAF arm				Control arm		
	D/C/F/TAF (baseline–week 48) ($N=362$)	D/C/F/TAF (week 48–week 96) ($N=335$)	D/C/F/TAF (baseline–week 96) ($N=362$)	P value[a,b]	D/C + F/TDF (baseline–switch) ($N=363$)	D/C/F/TAF (switch–week 96)[c] ($N=295$)	P value[a,b]
Patient-years exposure[d]	323	303	626		512	109	
Treatment-emergent adverse events [*n* (%)]							
AEs, any grade, regardless of causality	312 (86)	246 (73)	334 (92)	ND	326 (90)	125 (42)	ND
Study drug-related AEs	128 (35)	25 (7)	142 (39)	ND	158 (44)	14 (5)	ND
Grade 3–4 AEs regardless of causality	20 (6)	29 (9)	45 (12)	ND	33 (9)	15 (5)	ND
Study drug-related grade 3 or 4 AEs	6 (2)	7 (2)	11 (3)	ND	6 (2)	3 (1)	ND
Serious AEs regardless of causality	17 (5)	24 (7)	39 (11)	ND	36 (10)	8 (3)	ND
Study drug-related serious AEs	0	1 (<1)	1 (<1)	ND	6 (2)	0	ND
AE-related discontinuations	8[e] (2)	2[e] (1)	10[e] (3)	ND	17 (5)	1[e] (<1)	ND
Most common AEs regardless of causality (≥10% D/C/F/TAF arm through 96 weeks)							
Diarrhoea	72 (20)	23 (7)	83 (23)	ND	74 (20)	7 (2)	ND
Nasopharyngitis	40 (11)	26 (8)	58 (16)	ND	38 (10)	11 (4)	ND
Headache	48 (13)	12 (4)	54 (15)	ND	38 (10)	5 (2)	ND
Study drug-related AEs (all grades; ≥5% D/C/F/TAF arm through 96 weeks)							
Diarrhoea	33 (9)	2 (1)	34 (9)	ND	42 (12)	1 (<1)	ND
Rash	22 (6)	0	22 (6)	ND	14 (4)	1 (<1)	ND
Nausea	20 (6)	0	20 (6)	ND	36 (10)	3 (1)	ND
Most common treatment-emergent grade 3 or 4 laboratory abnormalities (>5% D/C/F/TAF arm through 96 weeks)							
Fasting LDL-cholesterol (≥4.90 mmol/l; ≥190 mg/dl)	17/345 (5)	22/330 (7)	30/346 (9)	ND	6/340 (2)	11/280 (4)	ND
Median (IQR) change in fasting lipids							
TC (mg/dl)	+28.6 (12.8–47.6)	ND	+34.0 (16.2–55.7)	<0.001	+10.4 (−8.0 to 29.8)	+21.8 (5.8–37.9)	<0.001
HDL-C (mg/dl)	+4.4 (−1.2 to 12.0)	ND	+5.0 (0.0– 12.0)	<0.001	+1.5 (−3.9 to 8.1)	+1.9 (−1.9 to 8.5)	<0.001
LDL-C (mg/dl)	+17.4 (3.0–33.3)	ND	+21.7 (5.8–42.2)	<0.001	+5.0 (−10.8 to 18.9)	+15.1 (1.0–29.0)	<0.001
Triglycerides (mg/dl)	+24.4 (−3.0 to 58.5)	ND	+29.2 (0.9– 64.7)	<0.001	+14.2 (−12.0 to 40.7)	+14.2 (−17.7 to 54.9)	<0.001
TC/HDL-C ratio	+0.20 (−0.28 to 0.67)	ND	+0.25 (−0.20 to 0.87)	<0.001	+0.08 (−0.41 to 0.53)	+0.24 (−0.19 to 0.72)	<0.001

AE, adverse event; D/C + F/TDF, darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate once daily; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide once daily; HDL-C, high-density lipoprotein-cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; ND, not determined; TC, total cholesterol.

[a]Within treatment arm comparisons for change at week 96 from reference assessed by Wilcoxon signed-rank test (fasting lipids).

[b]Reference for the D/C/F/TAF arm is study baseline and for the D/C/F/TAF switch arm is the last value before the switch.

[c]Respectively, 2.5, 41.3 and 36.4% of patients randomized to the control arm switched to D/C/F/TAF at week 60, week 72 and week 84.

[d]Patient years of exposure = sum of treatment duration (in weeks) × 7/365.25.

[e]D/C/F/TAF arm (baseline–week 48) ($n=8$): rash ($n=6$), diarrhoea ($n=2$); D/C/F/TAF arm (week 48–week 96) ($n=2$): viral hepatitis ($n=1$), pregnancy ($n=1$); Control arm (switch–week 96): rash ($n=1$).

week 96 in the D/C/F/TAF arm and 33 patients at week 96 in the control arm had data for $eGFR_{cyst}$ (CKD-EPI formula; [16]), so changes at week 84 are presented. The median (IQR) change from baseline to week 84 in $eGFR_{cyst}$ in the D/C/F/TAF arm ($n = 204$) was stable at +3.2 (−3.5 to 11.3) ml/min per 1.73 m^2 (Fig. 4b). The median (IQR) change in $eGFR_{cyst}$ at week 84 versus reference in the control arm ($n = 100$) was +1.2 (−3.2 to 6.4) ml/min per 1.73 m^2. In both arms, median $eGFR_{cr}$ and $eGFR_{cyst}$ were within normal limits through week 96.

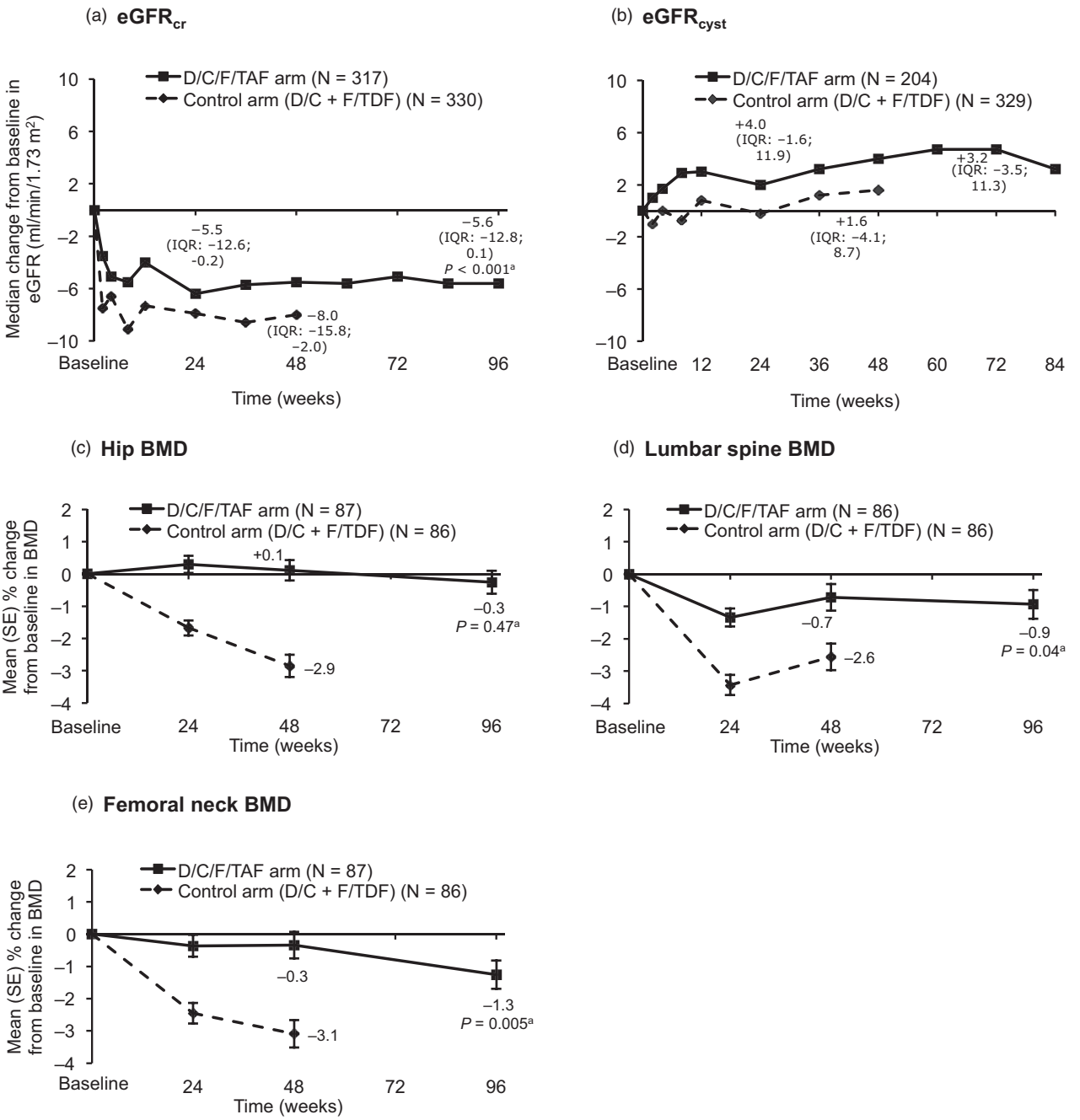


Fig. 4. Change from reference to week 48 and week 96 in renal and bone parameters. (a) $eGFR_{cyst}$ and (b) $eGFR_{cr}$ and BMD of the (c) hip, (d) lumbar spine and (e) femoral neck. BMD, bone mineral density; D/C + F/TDF, darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate once daily; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide once daily; $eGFR_{cr}$, estimated glomerular rate based on serum creatinine; $eGFR_{cyst}$, eGFR based on cystatin C; SE, standard error. [a]Within treatment arm for change at week 96 from baseline assessed by Wilcoxon signed-rank test (eGFR) and paired *t*-test (BMD). *N* is the number of evaluable patients in each treatment arm at week 96 (a, c, d and e) or week 84 (b).

In the D/C/F/TAF arm, improvements in proteinuria versus the control arm at week 48 were maintained through week 96. For example, Supplementary Figure 2a, http://links.lww.com/QAD/B597 shows that median change from baseline in UPCR at week 48 was −15.7 mg/g in the D/C/F/TAF arm and −10.5 mg/g in the control arm and at week 96 was −15.5 mg/g in the D/C/F/TAF arm. Similar trends were observed for median changes from baseline in UACR, RBP:Cr and B2M:Cr (Supplementary Figure 2a, http://links.lww.com/QAD/B597). In the control arm, decreases in all markers of proteinuria were observed at week 96 versus reference. Median (IQR) changes from reference to week 96 in UPCR were −1.4 (−15.0 to 9.9) mg/g, UACR −0.5 (−2.3 to 0.6) mg/g, RBP:Cr −35.5 (−88.2 to −2.9) μg/g and B2M:Cr −40.5 (−173.9 to −1.0) μg/g (all $P < 0.001$ except UPCR, $P = 0.112$).

Bone substudy

The bone substudy included 113 patients in the D/C/F/TAF arm and 99 in the control arm at baseline [5]. At week 48, mean change in BMD at each site was favourable for D/C/F/TAF versus control ([5]; Fig. 4c–e). In the D/C/F/TAF arm through week 96, there was no statistically significant change from baseline in hip BMD (Fig. 4c), with a small decrease in lumbar spine BMD (Fig. 4d) and femoral neck BMD (Fig. 4e; mean percentage change −0.3%, −0.9% and −1.3% at each site, respectively; $P = 0.47$ hip, $P = 0.04$ spine, $P = 0.005$ femoral neck). A similar trend was observed when comparing the relative proportions of patients who had at least 3%, at least 5% or at least 7% increases versus respective decreases in hip, spine and femoral neck BMD at weeks 96 versus baseline in the D/C/F/TAF arm (Supplementary Table 4, http://links.lww.com/QAD/B598).

In the control arm, there were numerical improvements at week 96 after switching to D/C/F/TAF compared with reference for hip (+0.5%), lumbar spine (+0.5%) and femoral neck BMD (+0.2%). Fewer patients had at least 3%, at least 5% or at least 7% decrease in BMD at each site at week 96 versus reference (following D/C/F/TAF switch) compared with the D/C plus F/TDF treatment phase, with more patients having at least 3% or at least 5% increases and similar proportions having at least 7% increases in BMD (Supplementary Table 4, http://links.lww.com/QAD/B598).

Conclusions were similar for the proportions of patients with an improvement (osteopenia to normal or osteoporosis to normal or osteopenia) or a worsening in BMD clinical status (normal to osteopenia or normal or osteopenia to osteoporosis) at each site (Supplementary Table 4, http://links.lww.com/QAD/B598).

In the D/C/F/TAF arm, there was no change in alkaline phosphatase and minimal changes in procollagen type N-terminal propeptide and C-type collagen sequence at week 96 from baseline indicating low bone turnover (Supplementary Figure 2b, http://links.lww.com/QAD/B597).

Discussion

This investigational phase 3, randomized trial in ART-naive patients showed that the once-daily D/C/F/TAF STR resulted in a high proportion of patients maintaining a virologic response of less than 50 copies/ml (FDA snapshot) at week 96 (85% D/C/F/TAF arm; 84% overall control arm) and low virologic failure rates (5.5 and 4.4%, respectively; FDA snapshot). Week 96 virologic response rates for D/C/F/TAF demonstrated here compare favourably with those for STRs in ART-naive patients from previous phase 3 trials (72–88%) [19–26]. Response rates in this trial were comparable across baseline patient subgroups, in the per-protocol and TLOVR analyses and using the 200 copies/ml cut-off. The high at least 95% cumulative adherence rate and improved adherence after switch from three pills (double-blind) to the open-label D/C/F/TAF STR in the control arm is in line with previous observations of improved treatment adherence with once-daily STRs compared with multitablet regimens [7–9].

No treatment-emergent DRV, primary protease inhibitor or tenofovir RAMs were detected through week 96, reaffirming the high efficacy and high genetic barrier to resistance of DRV-based initial ART observed previously [1,4,5]. The emtricitabine RAM M184I/V was detected in one patient at week 36 in the D/C/F/TAF arm, and M184V was detected in one patient at week 84 in the control arm (post switch to D/C/F/TAF). Resistance emergence in the D/C/F/TAF arm may have been related to transmitted drug resistance and suboptimal DRV concentration as reported previously [5,18]. The presence of M184I/V is not a contraindication to use of D/C/F/TAF. M184I/V RAMs increase tenofovir, stavudine and azidothymidine susceptibility and are associated with reduced viral replication *in vitro* and *in vivo* [27].

D/C/F/TAF may have an important role for treating patients with uncertain adherence or who plan to start treatment prior to the availability of resistance testing results [14,15]. D/C/F/TAF does not require HLA B*5701 screening, hepatitis or resistance testing before treatment initiation. At 48 weeks, D/C/F/TAF showed a high virologic response (84% of 109 patients) and 90% completed a phase 3, single-arm, rapid initiation study through 48 weeks (DIAMOND; NCT03227861) [28].

Low incidences of serious adverse events and discontinuations because of adverse events were observed and no deaths occurred, consistent with DRV and cobicistat

safety profiles [1–3,5,6,29–32]. No discontinuations because of bone, renal, or CNS adverse events occurred. All study drug-related diarrhoea events were grade 1 or 2 and mostly transient in duration.

A small increase in body weight was observed in the D/C/F/TAF arm over 2 years (2 kg), as observed in other studies in patients receiving ART [33] or switching from a TDF to a TAF regimen [34]. In ART-naive individuals, these increases may also be due in part to lifestyle changes and return to health effects. Large treatment cohorts (NEAT022 and NA-ACCORD) suggest that integrase inhibitors may be associated with more weight gain than protease inhibitors [35,36].

Renal, bone and lipid safety results were consistent with the established effects of TAF versus TDF [5,6,19,30]. In the current study through week 48, all quantitative measures demonstrated less proteinuria, improvement in $eGFR_{cyst}$ and more favourable hip, spine and femoral neck BMD and associated *T*-scores for D/C/F/TAF versus control [5]. Furthermore, the incidence of renal adverse effects regardless of causality was lower in the D/C/F/TAF arm (2%; 7/362) versus control (6%; 21/363) over 48 weeks [5]. Improvements in renal tubular proteinuria and BMD at each site seen in the D/C/F/TAF arm at week 48 versus control and preservation of eGFR were maintained through week 96 and observed in the control arm after switch through week 96. In the D/C/F/TAF arm, there were increases in fasting lipids at week 96. TDF decreases total cholesterol, LDL-C and HDL-C to a modest extent, and therefore, combination regimens containing TDF have less of an effect on cholesterol than TAF-containing therapy [5,6,19,30,37]. The difference in cholesterol between control and D/C/F/TAF at week 48 and the change in cholesterol in the control arm when switched after week 48 is likely because of the effects of TDF rather than an adverse effect of TAF or other components of D/C/F/TAF on lipids [38]. Whether the cholesterol-lowering effects of TDF has any clinical benefit is unknown. Only a small proportion of patients initiated lipid-lowering therapy in either arm (4% over 96 weeks in the D/C/F/TAF arm and 1% from switch through week 96 in the control arm).

A study limitation was the nonuniform D/C/F/TAF switch times in the control arm, resulting in a lack of benchmark for D/C/F/TAF exposure, and hence we focused on the efficacy results for the overall 96-week control arm. However, the most relevant data comes from the 96 weeks of D/C/F/TAF treatment in the experimental arm. In addition, adherence was assessed by pill count, which may not always capture true adherence [39,40]. An internationally agreed upon standard for measuring adherence does not exist, and pill count is a convenient, routinely used method for assessing adherence. Other limitations were similar to those for other recent phase 3 trials in ART-naive patients and limit generalizability of the results [20,21,23–26,41], such as inclusion of a comparatively small proportion of female patients, older patients (>50 years), nonwhite patients, and likely because of treatment guidelines recommending earlier initiation of ART, those with viral loads at least 100 000 copies/ml and $CD4^+$ counts <200 cells/μl.

In conclusion, D/C/F/TAF resulted in a high virologic response and low virologic failure rates (FDA-snapshot) at week 96, with no development of resistance to DRV or TAF in ART-naive adults. Week 96 safety findings were consistent with those at week 48. Bone, renal and lipid safety were consistent with known profiles of the D/C/F/TAF components. Control arm safety findings following D/C/F/TAF switch (limited exposure) were consistent with results in the D/C/F/TAF arm. The results of the AMBER phase 3 trial through 96 weeks confirm the efficacy and high genetic barrier to resistance and bone/renal safety advantages of D/C/F/TAF for ART-naive patients.

Acknowledgements

We thank the patients and their families for their participation and support during the study, the central and local Janssen AMBER study teams, study centre staff, and the AMBER principal investigators:

Belgium: S. De Wit, E. Florence, L. Vandekerckhove, B. Vandercam; Canada: J. Brunetta, M. Klein, D. Murphy, A. Rachlis, S. Walmsley; France: F. Ajana, L. Cotte, P.-M. Girard, C. Katlama, J.-M. Molina, I. Poizot-Martin, F. Raffi, D. Rey, J. Reynes, E. Teicher, Y. Yazdanpanah; Germany: K. Arastéh, M. Bickel, J. Bogner, S. Esser, G. Faetkenheuer, H. Jessen, W. Kern, J. Rockstroh, C. Spinner, H.-J. Stellbrink, A. Stoehr; Italy: A. Antinori, F. Castelli, A. Chirianni, A. De Luca, A. Di Biagio, M. Galli, A. Lazzarin, F. Maggiolo, R. Maserati, C. Mussini; Poland: A. Garlicki, J. Gasiorowski, W. Halota, A. Horban, M. Parczewski, A. Piekarska; Russia: E. Belonosova, O. Chernova, N. Dushkina, V. Kulagin, E. Ryamova, A. Shuldyakov, N. Sizova, O. Tsybakova, E. Voronin, A. Yakovlev; Spain: A. Antela, J.R. Arribas, J. Berenguer, J. Casado, V. Estrada, M.J. Galindo, M. Garcia Del Toro, J.M. Gatell, M. Gorgolas, F. Gutierrez, M.D.M. Gutierrez, E. Negredo, J.A. Pineda, D. Podzamczer, J. Portilla Sogorb, A. Rivero, R. Rubio, P. Viciana, I. De Los Santos; UK: A. Clarke, B.G. Gazzard, M.A. Johnson, C. Orkin, I. Reeves, L. Waters; US: P. Benson, L. Bhatti, F. Bredeek, G. Crofoot, D. Cunningham, E. DeJesus, J. Eron, F. Felizarta, R. Franco, J. Gallant, D. Hagins, K. Henry, D. Jayaweera, C. Lucasti, C. Martorell, C. McDonald, J. McGowan, A. Mills, J. Morales-Ramirez,

D. Prelutsky, M. Ramgopal, B. Rashbaum, P. Ruane, J. Slim, A. Wilkin, J. deVente.

We also thank other Janssen staff members for their input into this manuscript. We also acknowledge Ian Woolveridge (Zoetic Science, an Ashfield company, Macclesfield, UK) for assistance in drafting the manuscript and coordinating and collating author contributions, which was funded by Janssen. Week 96 data were presented in part at HIV14, 28–31 October 2018 in Glasgow, UK (abstract 0212). The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Contributors: C.O., J.E., J.R., D.P., S.E., and L.K. were investigators in the study and reported data for the patients. E.V.L., E.L., V.H., J.J., and M.O. were involved in the data analyses. All authors were involved in the development of the primary manuscript, interpretation of data, and have read and approved the final version, and have met the criteria for authorship as established by the ICMJE.

Conflicts of interest

This study was sponsored by Janssen. C.O. has received speaker honoraria or consulting fees for attending Speaker's Bureaus or advisory boards and research grants from Janssen, Merck, ViiV Healthcare and Gilead Sciences. J.E. received research grants from Janssen, Gilead Sciences and ViiV Healthcare and has served as a consultant to Bristol-Myers Squibb (BMS), Merck, Janssen, Gilead Sciences and ViiV Healthcare. J.R. has received honoraria for consulting or speaking at educational events from Abivax, AbbVie, Gilead Sciences, Janssen, Merck and ViiV Healthcare. D.P. has received research grants and/or honoraria for advisories and/or conferences from ViiV Healthcare, Gilead Sciences, Janssen and Merck. S.E. has received honoraria for lectures or advisory boards and his institution research grants from ViiV Healthcare, Gilead Sciences, Merck and Janssen. L.V. has received research grants and/or honoraria for advisories and/or conferences from ViiV Healthcare, Gilead Sciences, Janssen and Merck. E.V.L., E.L., V.H., J.J. and M.O. are all full-time employees of Janssen and potential stockholders of Johnson and Johnson.

References

1. Orkin C, DeJesus E, Khanlou H, Stoehr A, Supparatpinyo K, Lathouwers E, *et al*. **Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial.** *HIV Med* 2013; **14**:49–59.
2. Cahn P, Fourie J, Grinsztejn B, Hodder S, Molina JM, Ruxrungtham K, *et al*. **Week 48 analysis of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients.** *AIDS* 2011; **25**:929–939.
3. Flynn P, Komar S, Blanche S, Giaquinto CS Noguera-Julian A, Welch S, *et al*. **Efficacy and safety of darunavir/ritonavir at 48 weeks in treatment-naive, HIV-1-infected adolescents: results from a phase 2 open-label trial (DIONE).** *Pediatr Infect Dis J* 2014; **33**:940–945.
4. Lathouwers E, Wong EY, Luo D, Seyedkazemi S, De Meyer S, Brown K. **HIV-1 resistance rarely observed in subjects using darunavir once-daily regimens across clinical studies.** *HIV Clin Trials* 2017; **18**:196–204.
5. Eron J, Orkin C, Gallant J, Molina JM, Negredo E, Antinori A, *et al*. **A week 48 randomized phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients.** *AIDS* 2018; **32**:1431–1442.
6. Orkin C, Molina J-M, Negredo E, Arribas JR, Gathe J, Eron JJ, *et al*., EMERALD study group. **Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine/tenofovir disoproxil fumarate regimens to the once-daily complete HIV-1 regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in virologically suppressed, HIV-1-infected adults through 48 weeks (EMERALD): a phase 3, randomized, noninferiority trial.** *Lancet HIV* 2018; **5**:e23–e34.
7. Nachega JB, Marconi VC, van Zyl GU, Gardner EM, Preiser W, Hong SY, *et al*. **HIV treatment adherence, drug resistance, virologic failure: evolving concepts.** *Infect Disord Drug Targets* 2011; **11**:167–174.
8. Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. **Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era.** *Patient Prefer Adherence* 2012; **6**:427–433.
9. Clay PG, Nag S, Graham CM, Narayanan S. **Meta-analysis of studies comparing single and multitablet fixed dose combination HIV treatment regimens.** *Medicine (Baltimore)* 2015; **94**:e1677.
10. SYMTUZA™ (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets: summary of product characteristics. Janssen-Cilag International NV, 2017. Revised: July 2019. Available at: https://www.medicines.org.uk/emc/product/8430. [Accessed 24 January 2020]
11. Prescribing information for SYMTUZA™ (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets. Janssen Pharmaceutical Companies, 2018. Revised: May 2019. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SYMTUZA-pi.pdf. [Accessed 24 January 2020]
12. Eron JJ, Orkin C, Cunningham D, Pulido F, Post FA, De Wit S, *et al*., EMERALD study group. **Week 96 efficacy and safety results of the phase 3, randomized EMERALD trial to evaluate switching from boosted-protease inhibitors plus emtricitabine/tenofovir disoproxil fumarate regimens to the once daily, single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in treatment-experienced, virologically-suppressed adults living with HIV-1.** *Antivir Res* 2019; **170**:104543.
13. EACS. European AIDS Clinical Society Guidelines, Version 10.0. November 2019. Available at: https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf. [Accessed 24 January 2020]
14. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services (Updated December 18 2019). Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. [Accessed 24 January 2020]
15. Saag MS, Benson CA, Gandhi RT, Hoy JF, Landovitz RJ, Mugavero MJ, *et al*. **Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel.** *JAMA* 2018; **320**:379–396.
16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al*., CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). **A new equation to estimate glomerular filtration rate.** *Ann Intern Med* 2009; **150**:604–612.
17. Wensing AM, Calvez V, Gunthard HF, Johnson VA, Paredes R, Pillay D, *et al*. **Update of the drug resistance mutations in HIV-1: June/July 2014.** *Top Antivir Med* 2014; **22**:642–650.

18. Lathouwers E, Wong EY, Brown K, Baugh B, Ghys A, Jezorwski J, *et al*. **Week 48 resistance analyses of the once-daily, single-tablet regimen (STR) darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in adults living with HIV-1 from the Phase 3 randomised AMBER and EMERALD trials.** *AIDS Res Hum Retroviruses* 2020; **36**:48–57.
19. Wohl D, Oka S, Clumeck N, Clarke A, Brinson C, Stephens J, *et al*., GS-US-2,92-01040111 and study team. **Brief Report: A randomized, double-blind comparison of tenofovir alafenamide versus tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: week 96 results.** *J Acquir Immune Defic Syndr* 2016; **72**:58–64.
20. van Lunzen J, Antinori A, Cohen CJ, Arribas JR, Wohl DA, Rieger A, *et al*. **Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study.** *AIDS* 2016; **30**:251–259.
21. Zolopa A, Sax PE, DeJesus E, Mills A, Cohen C, Wohl D, *et al*., GS-US-236-0102 study team. **A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results.** *J Acquir Immune Defic Syndr* 2013; **63**:96–100.
22. Rockstroh JK, DeJesus E, Henry K, Molina JM, Gathe J, Ramanathan S, *et al*., GS-236-0103 study team. **A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results.** *J Acquir Immune Defic Syndr* 2013; **62**:483–486.
23. Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-Josses MA, *et al*. **Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial.** *J Acquir Immune Defic Syndr* 2015; **70**:515–519.
24. Stellbrink HJ, Arribas J, Stephens JL, Albrecht H, Sax PE, Maggiolo F, *et al*. **Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, noninferiority trial.** *Lancet HIV* 2019; **6**:e364–e372.
25. Wohl DA, Yazdanpanah Y, Baumgarten A, Clarke A, Thompson MA, Brinson C, *et al*. **Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, noninferiority trial.** *Lancet HIV* 2019; **6**:e355–e363.
26. Orkin C, Squires K, Molina J-M, Sax P, Wong W, Sussmann O, *et al*. **Doravirine/lamivudine/tenofovir DF continues to be noninferior to efavirenz/emtricitabine/tenofovir DF in treatment-naive adults with HIV-1 infection: week 96 results of the DRIVE-AHEAD trial**. *IDWeek Oct. 3-7, 2018b, in San Francisco*. Abstract and oral presentation LB1.
27. Stanford University HIV drug resistance database. Available at: https://hivdb.stanford.edu/dr-summary/resistance-notes/NRTI/. [Accessed 24 January 2020]
28. Huhn GS, Crofoot G, Ramgopal M, Gathe J Jr, Bolan R, Luo D, *et al*. **Darunavir/cobicistat/emtricitabine/tenofovir alafenamide in a rapid initiation model of care for HIV-1 infection. Primary analysis of the DIAMOND study**. *Clin Infect Dis* 2019 [Epub ahead of print].
29. Tashima K, Crofoot G, Tomaka FL, Kakuda TN, Brochot A, Van de Casteele T, *et al*. **Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial.** *AIDS Res Ther* 2014; **11**:39.
30. Mills A, Crofoot G Jr, McDonald C, Shalit P, Flamm JA, Gathe J Jr, *et al*. **Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study.** *J Acquir Immune Defic Syndr* 2015; **69**:439–445.
31. Elion R, Cohen C, Gathe J, Shalit P, Hawkins T, Liu HC, *et al*., GS-US-216-0105 Study Team. **Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir DF in the initial treatment of HIV infection.** *AIDS* 2011; **25**:1881–1886.
32. Gallant JE, Koenig E, Andrade-Villanueva J, Chetchotisakd P, DeJesus E, Antunes F, *et al*. **Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results.** *J Infect Dis* 2013; **208**:32–39.
33. Taramasso L, Ricci E, Menzaghi B, Orofino G, Passerini S, Madeddu G, *et al*., CISAI Study Group. **Weight gain: a possible side effect of all antiretrovirals.** *Open Forum Infect Dis* 2017; **4**:ofx239.
34. Gomez M, Seybold U, Roider J, Härter G, Bogner JR. **A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015-2017.** *Infection* 2019; **47**:95–102.
35. Waters L, Assoumou L, Rusconi S, Domingo P, Gompels M, de Wit S, *et al*. **Switch to dolutegravir (DTG) from a boosted protease inhibitor (PI/r) associated with significant weight gain over 48 weeks in NEAT-022, a randomised 96-week trial**. *HIV Drug Therapy, Glasgow, 28–31 October 2018*. Abstract and poster P102.
36. Bourgi K, Jenkins C, Rebeiro PF, Castilho JL, Hulgan T, Raffanti SP, *et al*. **Greater weight gain among treatment-naive persons starting integrase inhibitors**. *Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, Washington, 4–7 March 2019*. Abstract and poster 670.
37. Cid-Silva P, Fernández-Bargiela N, Margusino-Framiñán L, Balboa-Barreiro V, Mena-De-Cea A, López-Calvo S, *et al*. **Treatment with tenofovir alafenamide fumarate worsens the lipid profile of HIV-infected patients versus treatment with tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine.** *Basic Clin Pharmacol Toxicol* 2019; **124**:479–490.
38. Tungsiripat M, Kitch D, Glesby MJ, Gupta SK, Mellors JW, Moran L, *et al*. **A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206.** *AIDS* 2010; **24**:1781–1784.
39. Almeida-Brasil CC, Moodie EEM, Cardoso TS, Nascimento ED, Ceccato MDGB. **Comparison of the predictive performance of adherence measures for virologic failure detection in people living with HIV: a systematic review and pairwise meta-analysis.** *AIDS Care* 2019; **31**:647–659.
40. Martelli G, Antonucci R, Mukurasi A, Zepherine H, Nöstlinger C. **Adherence to antiretroviral treatment among children and adolescents in Tanzania: Comparison between pill count and viral load outcomes in a rural context of Mwanza region.** *PLoS One* 2019; **14**:e0214014.
41. Molina JM, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, *et al*., FLAMINGO study team. **Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study.** *Lancet HIV* 2015; **2**:e127–136.